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13. ABSTRACT *(Maximum 200 words)*

We are progressing well toward the grant's original goals. Personnel attrition and software changes have impeded progress so we have obtained a one year no-cost extension. We have been productive none the less. We have developed finite element code to simulate the displacement of tissue from low frequency harmonic vibrations. The simulations showed us several things. First, when the amplitude of the vibration is large enough to measure accurately with the MRI, the solutions become very complicated and require a partial differential equation to estimate the elasticity; estimates of elasticity that only use local data are only useful for very simple geometry with very simple boundary conditions. Second, shear waves are damped much faster than distortional waves so we have designed a vibration source capable of inducing compression and shaking rather than shear. We have designed, built and tested the device that produces wide bandwidth, high force, high amplitude displacements in an MRI magnet. The device is non-resonant so arbitrary waveforms can be achieved. We have rewritten the MR pulse sequences for the newest MRI scanner. We have developed a reconstruction routine that successfully reconstructs simulated elasticity distributions. The results are substantive progress toward the goals of this project.

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FOREWORD

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MR Measurement of Breast Tissue's Anisotropic Mechanical Properties: Breast Cancer Detection and Classification

Introduction:

We are developing a magnetic resonance (MR) method of measuring the mechanical properties of tissue, including the hardness, quantified by the three dimensional (3D) modulus of elasticity, and the density. Tissue is vibrated at low frequency and the displacement of the tissue will be measured with MR imaging. The mechanical properties of the breast will be calculated from the measured displacements via a partial differential equation describing the motion. We will measure the elasticity in all three directions by vibrating the tissue in all three directions and measuring the resulting three dimensional displacements. Measuring the 3D elasticity is important because fibrous tissue is anisotropic which suggests that the elasticity of the breast itself will be anisotropic.

Elasticity measurements might play several roles in breast cancer detection and in evaluating treatment effectiveness. Elasticity may help classify lesions identified with mammography which is sensitive but not specific; roughly two thirds of the lesions detected with mammography turn out, on biopsy, to be neither malignant nor pre-malignant [1]. Secondly, because mammography can not detect all palpable lesions [2], elasticity measurements could supplement the physical examination and mammography in screening programs. The sensitivity of mammography with current technology is between 85% and 90% [3]. Elasticity measurement should be used as part of the screening examination if it catches some significant fraction of the missed malignancies. Abnormalities such as architectural distortions which are often missed in mammography [4] should be well visualized with elasticity measurements. We are developing 3D elasticity measurements to determine its usefulness in classification and screening. Once tissue properties are measured for a variety of tumors and benign lesions, less expensive methods can be developed that are designed to measure the relevant tissue properties.

Several groups have been working to estimate the elasticity. Tissue elasticity estimates are being made with static distortion measured with MR [5] and ultrasound [6,7] and with dynamic distortion measured with MR [8,9,10] and ultrasound [11,12]. However, some of those estimates are made assuming a plane wave which, as we show, is not a good assumption. We have been developing a method using dynamic distortion measured with MR phase contrast imaging. We are using dynamic distortion because damping and other "resistive" effects can be estimated using the change in elasticity with frequecncy of vibration. We are pursueing a different course from the other groups using MR and dynamic distortion in that we are using the partial differential equation governing elastic distortion to estimate the elasticity from the measured displacements.

Body:

Our long term hypothesis is that elasticity estimates will 1) contribute toward the accurate classification of lesions detected with mammography and 2) detect a significant number of the malignancies missed by mammography. The hypothesis we are testing in this proposal is that we can measure the mechanical properties of tissue with MR using a linear, lossless motion model. We are also establishing that the properties measured completely describe the vibration of tissue so there is no other information to be gained from measurements of vibration. This is important to establish before trials with patients are started so the correct measurements are made.

The statement of work in the original proposal with the status beside each item is given below:

Technical Objective 1: Refine the MR measurement of three dimensional displacement during vibration.	
Months 1-6: Build the high power, low noise apparatus to measure the three dimensional displacement during vibration.	Completed
Months 6-8: Compare the measured displacement to measurements from a calibrated hydrophone and tune the system.	Partially Completed
Technical Objective 2: Compare the elasticity calculated from the MR displacements with a linear model to known elasticity's for isotropic and anisotropic materials.	Completed
Month 7: Modify the scale with the vernier to measure the elasticity manually with a mechanical method.	Initiated
Months 8-12: Build phantoms and compare the elasticity calculated from the MR displacements with a linear model to known elasticity's for isotropic and anisotropic materials.	Partially Completed
Technical Objective 3: Establish the limits of the linear, lossless elastic model of tissue motion during vibration.	
Months 10-14: Find the dependence of MR elasticity on the frequency and amplitude of the vibration.	Completed
Months 15-19: Measure motion perpendicular to the direction of forced vibration.	Completed
Months 20-24: Measure viscous losses by the attenuation of the vibration across the material.	Initiated
Months 13-15: Develop and test finite element code to calculate the displacement.	Completed

Compare the measured displacements with the displacements calculated with a finite element analysis for: Months 16-18: Phantoms with simple geometry. Months 18-20: Complicated phantoms. Months 20-22: Lean meat (probably a roast). Months 21-24: Meat with fat and muscle (probably a slab of bacon).	All Partially Completed

The specific technical objectives we planned for the first year of the project were:

1) Refine the MR measurement of three-dimensional displacement during vibration.
2) Compare the elasticity calculated from the MR displacements with a linear model to known elasticity's for isotropic and anisotropic materials.

The specific technical objectives we planned for the second year of the project were:

3) Establish the limits of the partial differential equations governing the distortion of elastic materials.

The third technical objective was divided into several parts:

a) Evaluate of the frequency dependence of the elasticity.
b) Evaluate motion perpendicular to the direction of forced vibration.
c) Evaluate viscous losses across phantom materials.
d) Compare the measured displacements with those calculated from a finite element solution of the equations governing the distortion of elastic materials.

We have had personnel and equipment problems that have significantly impeded the progress of the project. The postdoc hired for this project left after five months for a higher salary in industry. He accomplished very little in his five month tenure because most of his time was in training. We have gotten a graduate student in to work on the project but he had to be trained as well. This has cost us significant amounts of time. We have also had two major software and hardware upgrades to the scanner used for research in fourteen months: from 4.x software to 5.x software and then to 8.x software four months ago. Each update allowed the sequences to be improved and the last update allowed the gradient strength to be doubled but each new version of software required a the sequences to be coded from the GE distribution sequences which required time.

However, we have been productive none the less. We have had six significant accomplishments in the last year.

1) Rewritten MR sequences for the new MR system software using faster and stronger gradients.

2) Produced a wide bandwidth vibrator capable of producing large forces and large displacements. Evaluated the vibrator.
3) Produced finite element code to simulate harmonic displacements. Studied simulations of displacements with finite element model [13].
4) Developed a method of calculating the elasticity from the displacements without assuming a plane wave geometry. Reconstructed elasticity from simulated displacements [13].
5) Developed elastic alignment methods [1415,16,17] estimate the distortion field in going from an image of the anatomy to another image of the anatomy which has been mechanically distorted. The elasticity can be found from the distortion fields with the same methods as are used in the ultrasound methods [6,7].
6) Introduced and developed monotonic noise reduction [18,19,20,21,22]. The primary application is to increase the accuracy of phase angle measurements by reducing noise. The method works well at low signal to noise ratios (SNRs) and can increase the SNR of the phase by a factor of ten or more [19].

In terms of the specific aims of the project, we have accomplished: number 1for the new MRI system, number 2 using the finite element methods, and numbers 3b,c,d using finite element methods.

The remainer of this section will be organized develop and give details of the six accomplishments given above.

The MRI system sequences changed significantly between 4.x, 5.x and 8.x and we have tried to keep up with those changes. The latest version of hardware has significantly larger gradients than previous versions which will increase the sensitivity and flexibility of the displacement measurements. We have had the 8.x system for 5 and a half months and have had 8.x EPIC programming for 3 months. We have sequences running and have obtained images. However, there are RF artifacts that need to be eliminated (see appendix). We could work around the artifacts by offsetting the field of view (FOV) if necessary but we would rather eliminate it altogether. The RF artifacts can be eliminated by blanking one of the RF pulses. We are now changing the "addrfbits.c" routine in the EPIC compiler to allow the RF pulse to be blanked. GE was somewhat reticent to give out the source code for the EPIC compiler but they finally did so 3 weeks ago. We are almost ready to measure displacements which is where we were with the 4.x system 14 months ago.

We have designed, built and tested a system to vibrate a sample in the magnet. The system produces large forces (3000 newtons). The displacement can be 42 microns when sufficient current is produced. The vibrator consists of three stacks of three piezoelectric actuators[1]. Each stack of actuators in each stack to provide sufficient displacements; each

[1] The individual actuators were purchased from Piezo Systems Inc.

stack is capable of producing 14 microns displacement. There are three stacks because the stacks are so thin. If the center of mass is off the center of the stack, a tension is placed on the other side of the stack which pulls the layers in the actuator apart. The center of mass of the sample can not be known accurately without extensive measurements which are not practical. With three stacks the center of mass can be essentially anywhere between the three. We put plates of very stiff material (Aremcolox, a barium glass/ mica / amorphous silica ceramic, 40,000 psi compressive strength) between each layer in the stack to add stability. The system is mechanically stable for a wide variety of loads.

We used a focused laser to measure the displacements produced by the device. The laser was focused down to a as small a point as possible using a lens. A photodiode is used to detect the laser light. The vibrator moves a knife edge into the laser light where it is most tightly focused. When the knife cuts off more of the laser light, the output of the photodiode drops. The output of the photodiode was calibrated using a knife edge on a micrometer. The system works very well and is easier to use than a system that deflects the laser beam over a large distance which has been used in previous studies [9]. The outputs for several input frequencies and several input voltages were measured (see appendix 1, page 16). The output was 10 microns at 100 Hz and 50 volts. The waveform degenerated if larger voltages were used because the amplifier was current limited; it is unable to generate sufficient current at that voltage and frequency. At lower frequencies the displacement was larger. However, we can not drop the current much lower than 100 Hz using the current MR pulse sequences because the echo times become too long. A second amplifier would increase the current generated and therefore the displacement generated by a factor of two. However, we can see sufficient phase changes using 10 micro displacements so we are not going to buy a second amplifier yet.

We are also preparing a digital output to measure the frequency response of the vibrator. We are planning to put a square wave into the amplifier and measure the distortion of the displacement waveform to get the frequency response over a wide range of frequencies.

We have written and tested finite element code to calculate the harmonic vibrations in elastic media [23]. We studies the classic treatments of waves in elastic media [24,25]. We used the full equation governing elastic distortion in the frequency domain:

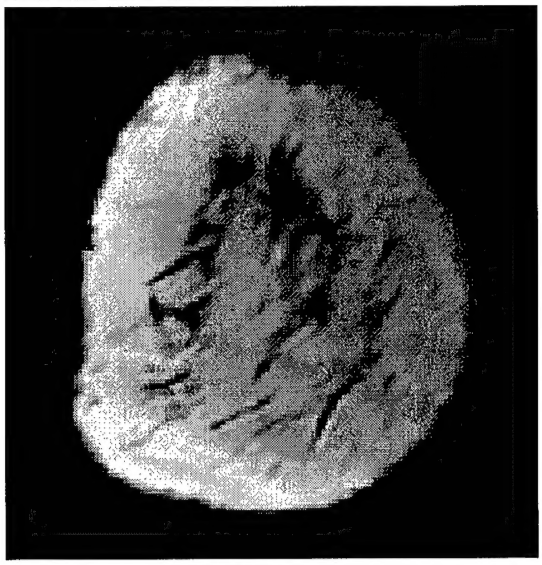
$$\nabla \cdot G\nabla \vec{u} + \nabla \frac{G}{1-2\upsilon}(\nabla \cdot \vec{u}) = \rho\omega^2 \vec{u} \qquad \text{Equation 1}$$

The finite element code has been written in both two and three dimensions. The results provided here are in two dimensions.

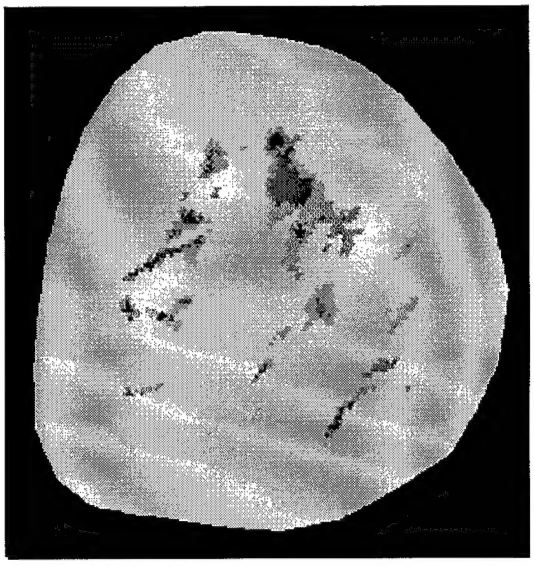
We have simulated vibration in regular geometry (bars) and breast geometry taken from clinical scans. Vibration from compression, shaking, and shear have all been simulated. Various boundary conditions have also been studied. The effects of damping have also been simulated.

We have reached 4 general conclusions from the simulations we have run:
1) If the driving displacement is large enough to obtain 3D MR phase contrast images in reasonable times, there is likely to be significant displacement in directions perpendicular to the direction of the driving force.
2) Multi-dimensional displacement (e.g. in directions other than in-line with the driving force) requires partial differential equation solution to adequately describe the displacement field.
3) Because partial differential equations are necessary to describe the motion, those equations must be used to estimate the elasticity.
4) Shear waves are damped much faster than distortional waves so we have designed a vibration source capable of inducing compression and shaking rather than shear.
Some of the results of the simulations are given in the presentation to the American Association of Physicists in Medicine (AAPM)[13] in the appendix 2 (page 19).

We have developed a method of estimating the elasticity from the displacements measured with MR. Because the displacements in equation 1 are known, the elasticity can be estimated directly. We have run simulations to demonstrate. We took a clinical breast examination to give an axial slice through the breast. Two types of tissue were assumed: fatty background and glandular tissue was taken to be the pixels with intensities below a threshold. The glandular tissue was assumed to have a Young's modulus twice that of the fatty tissue. The displacements were calculated with the finite element code. The original scans and the finite element model are shown below.

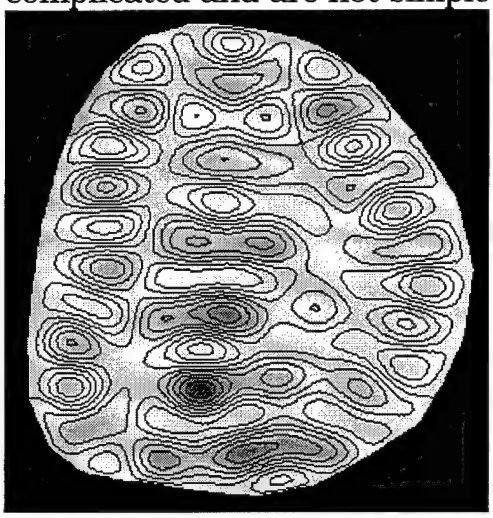


MR SCAN

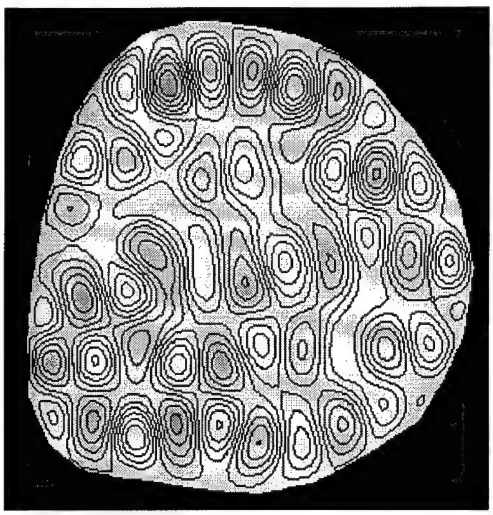


FEM Model

The calculated displacements are shown below. The displacments are complicated and are not simple plane waves.

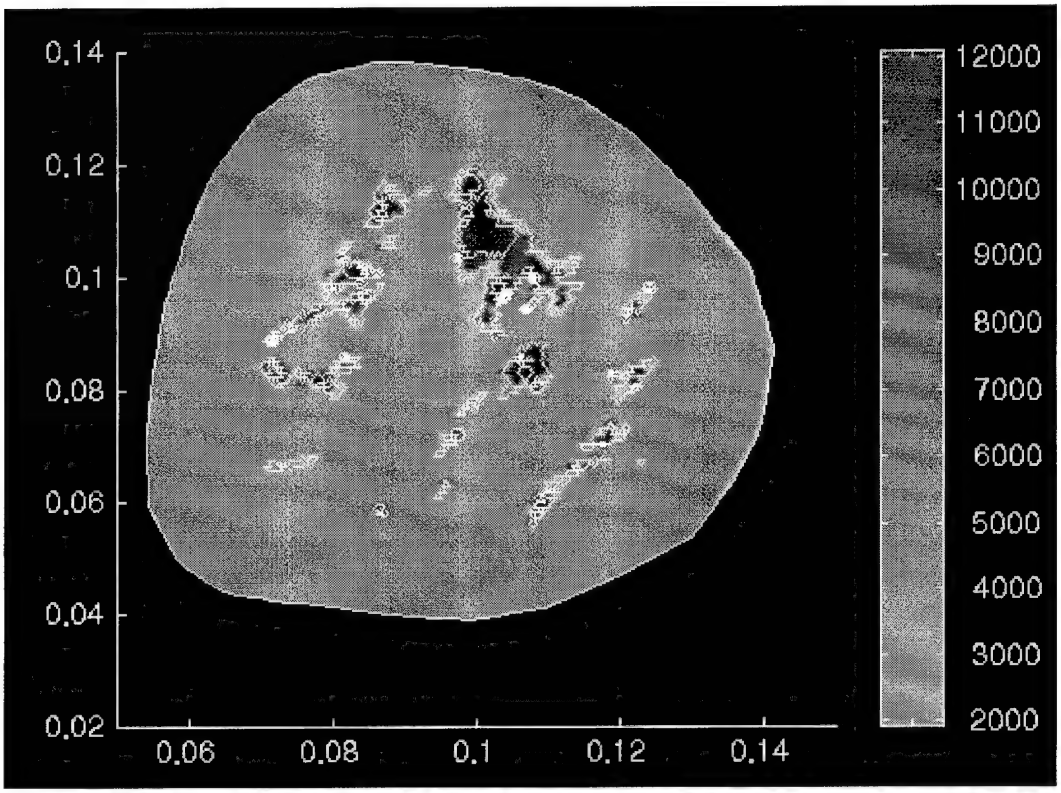


U_x



U_y

The elasticity was then reconstructed from the calculated displacements. The results are shown below.



Reconstructed Modulus: 2 Region Problem

The reconstructed modulus of elasticity closely matches the original distribution. This method of reconstruction does not depend on a plane wave as previous methods do. However, more study is necessary as to the methods stability and robustness.

Ultrasound image matching methods using static distortion have been used to estimate distortion and the elasticity from the distortion. We have begun to think about estimating distortion from MR images and using elastic matching to estimate distortion. Then the elasticity can be estimated from the distortions. We are not putting large amounts of effort into this yet. However, we have developed some very useful elastic matching routines [14-17] that are listed in the references and we are doing some preliminary studies on using these to estimate elasticity.

One of the biggest problems we encountered in the first year of working with low amplitude displacements was noise in the data. The phase changes were on the order of the noise. We have increased our displacements to eliminate this problem but we also developed a noise reduction technique that works much better than wavelet methods at low

SNRs. Monotonic noise reduction is capable of increasing the SNR of the phase angle by factors ranging from two to ten [19].

Conclusions:

Despite significant delays we are progressing well toward the original goals delineated in the grant. The issues have changed slightly as problems we did not foresee were more problematic than the problems we foresaw.

Our results suggest that a PDE is necessary to calculate the elasticity from vibration of materials at low frequencies. Shear waves seem to be damped much more than distortional waves so we have designed our apparatus to produce distortional waves. We have developed an apparatus that generates large displacements and large forces in the MR. We have also developed finite element methods to model low frequency vibrations. Preliminary results on a method to reconstruct the elasticity from measured displacements have been presented. That method uses the complete PDE instead of assuming the vibrations are plane waves.

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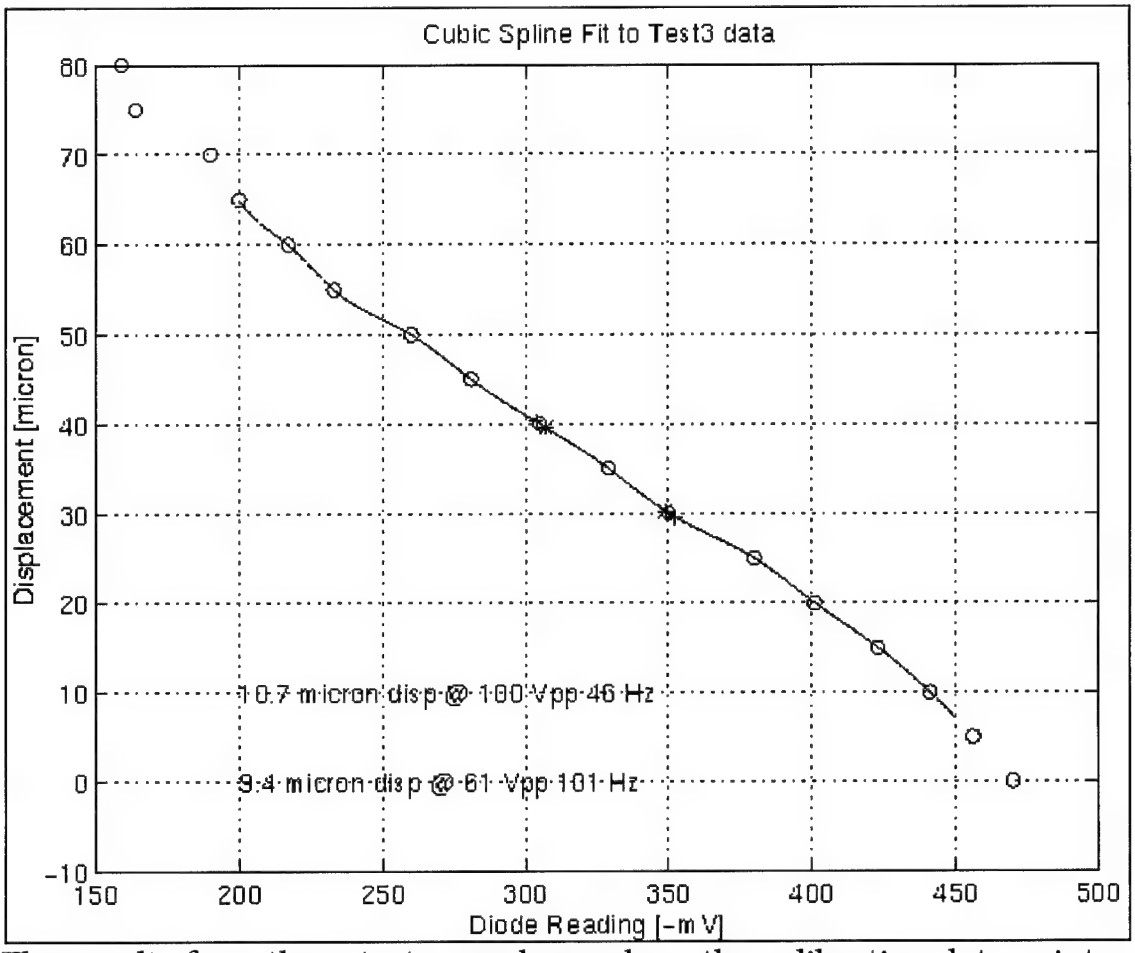
Appendix 1
Vibrator Displacement Measurements:

The piezoelectric actuator displacement capabilities were estimated by using the actuator motion to obstruct photon transmission from a 35 mW He - Ne laser. The laser was set up so that it's beam path was perpendicular to the direction of actuator displacement. The beam size was then reduced by a 10x optical lens, and the actuator was positioned so that it's motion would cut off the beam near or at it's focal point. A light collecting diode was placed on the opposite side of the actuator from the laser and positioned such that it collected the total beam, with little (if any) of the diode face unexposed to the beam. The actuator was placed on a micromotion translation table and the system was calibrated by reading the response from the diode to 5 micron incremental motions produced by the translation table. This was necessary due to the fact that photon density has a Gaussian distribution across the width of a laser beam. Once the beam was calibrated, the actuator, given a 60 V DC signal, was moved to a random position in the beam and a diode reading was taken to gauge this initial location. The actuator was then set to vibrate at either 100 Hz or 50 Hz (with an excitation of about 60 Vp-p or 100 Vp-p respectively). While the actuator was vibrating, the corresponding peak to peak voltage from the diode was taken, this voltage corresponding the to the total amount of displacement generated by the actuator. This experiment was repeated 4 times, each with a different calibration curve and tests at 100 Hz and 50 Hz.

These experiments were analyzed by first fitting a cubic spline to the calibration data points (consisting of position vs. diode voltage readings) so that actuator position could be accurately interpolated between these points. After the spline was fit, the initial position was determined from the initial diode reading, and then the maximum and minimum positions were determined from the peak to peak diode voltage information. Subtracting the minimum position from the maximum position gave an estimate to the total displacement created by the actuator.



The results from these tests are above where the calibration data points, the cubic spline fit, and the diode readings during actuator motion are shown.

The information from these analyses were then combined to develop an understanding of the actuator's behavior at differing excitation Voltages. The total actuator displacement vs. peak to peak excitation Voltage information was plotted as data points.

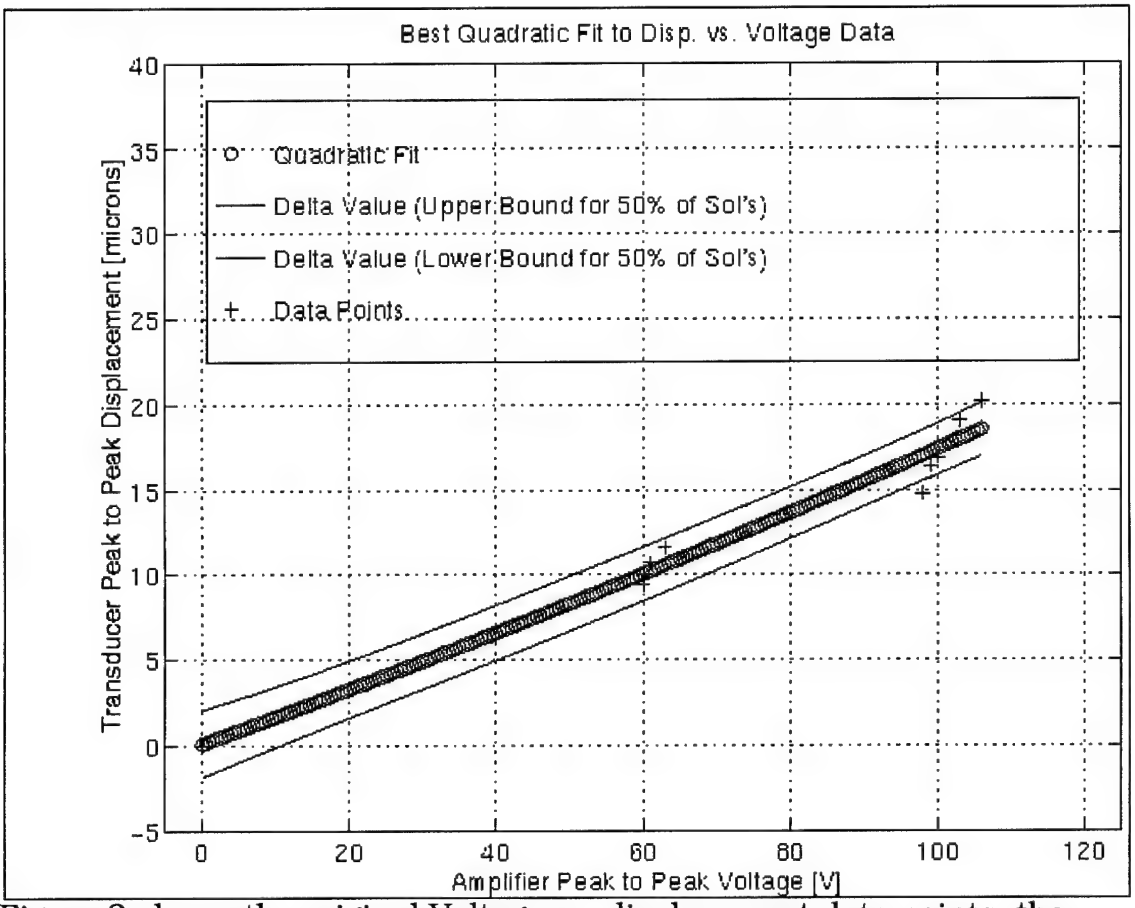


Figure 2 shows the original Voltage vs. displacement data points, the polynomial fit curve, and upper and lower bounds containing 50% of polynomial fit solutions to give an error estimation.

Elasticity estimates using phase contrast MRI measurements of displacement.

by
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Abstract

We are studying methods of reconstructing the elasticity from phase contrast MRI measurements of tissue vibration. There has been significant interest in estimating tissue elasticity from MRI phase contrast measurements of periodic and quasi-static displacement. MRI seems to hold more promise than ultrasound because of its ability to measure small tissue displacements simultaneously in all three directions resulting from a single mechanical stimulus while ultrasound is limited to recording tissue displacements in one preferred direction at a time.

We have calculated tissue displacements with the partial differential equations describing dynamic and static elastic deformation. Models of the breast were generated from MRI scan data. We have performed simulations for various modes of vibration. These simulations have led to three conclusions which impact how estimates of elasticity can be obtained from displacement fields:

1) If the driving displacement is large enough to obtain 3D MR phase contrast images in reasonable times, there is likely to be significant displacement in directions perpendicular to the direction of the driving force.

2) Multi-dimensional displacement (e.g. in directions other than in-line with the driving force) requires partial differential equation solution to adequately describe the displacement field.

3) Because partial differential equations are necessary to describe the motion, those equations must be used to estimate the elasticity.

If the displacement is all essentially in the direction of the driving force, simple local estimates of the elasticity would be possible.

Introduction

Mechanical measurements have tremendous promise because of the success of the physical examination in breast cancer screening. Elasticity measurements can play several roles in breast cancer detection and in evaluating treatment effectiveness. Elasticity may help classify lesions identified with mammography. Mammography is sensitive but not specific; roughly two thirds of the lesions detected with mammography turn out, on biopsy, to be neither malignant nor pre-malignant [Sickles et.al. 1990]. Secondly, because mammography can not detect all palpable lesions [Foster et. al. 1992, Kopans 1993], elasticity measurements could supplement the physical examination and mammography in screening programs. The sensitivity of mammography with current technology is between 85% and 90% [Bird 1990]. Elasticity measurement should be used as part of the screening examination if it catches some significant fraction of the missed malignancies. Abnormalities such as architectural distortions which are often missed in mammography [Bird et. al. 1992] should be well visualized with elasticity measurements. Tissue elasticity estimates are being made with static distortion measured with MR [Chenevert et al, 1998] and ultrasound [Ophir et al, 1991; Ponnekanti et al, 1995] and with dynamic distortion measured with MR [Muthupillai et al, 1995, 1996a 1996b] and ultrasound [Parker et al, 1990; Gao et al, 1995]. However, some of those estimates are made assuming a plane wave which, as we show, is not a good assumption.

Large displacements (e.g. approximately 0.01 mm) are needed to obtain fast and accurate measurements in the clinical setting. We show that under these conditions the motion of breast tissue is complex. Therefore, we are developing finite element model-based methods [Paulsen et. al. 1998; Miga et. al. 1998], to recover the localized mechanical properties of tissue which are indirectly linked to local tissue motion.

Methods:

Finite element code was used to calculate the displacements produced throughout samples with known mechanical properties. The equation modeled by the finite element code describes waves in elastic media in the frequency domain:

$$\nabla \cdot G\nabla\vec{u} + \nabla\frac{G}{1-2\upsilon}(\nabla\cdot\vec{u}) = \rho\omega^2\vec{u}$$

All excitations described here are steady state, harmonic solutions. All solutions were assumed to be plane stress; i.e., it is assumed that there are no z-direction stresses. We have used other frequencies but all solutions presented here are driven at 100 Hz. The vibrations we have explored include in phase compression (shaking) and shear that we show here as well as out of phase compression (squeezing) and others.

We show solutions on two physical models: 1) a simple bar to explore simple waves that one might expect in regular geometry's and 2) an axial slice of a breast. The geometry of the breast model was taken from a clinical scan. The background was taken to be fatty tissue with Young's modulus of 6000 Pa, a density of 1.02 gm/ml and a poison's ratio of 0.49. The glandular tissue was taken to be all tissue below a given threshold in the MR scan. Solutions were obtained with the glandular tissue having Young's modulus of 2 to 10 times that of the fatty tissue.

Our reconstruction method is based on finite element solution for the displacement field using the equations of linear elasticity. Calculated displacements were generated by the finite element model with known tissue property distributions. In this case, the two region problem was used with the background of fatty tissue and glandular tissue with twice the Young's modulus. The tissue density was assumed to be constant but can be solved for if necessary.

The displacement values at each node in the finite element mesh were used to recover the property data. Since the displacement field is sampled throughout the breast by the MR measurements it is known for the solution. We exploited the finite element method as a vehicle for discretizing the differential operators leaving only the property values as unknowns. If the tissue density is known (or approximated), the vibrational stimulus elicits a local force which can be directly deduced from the displacement measurements which in turn can be related to the discrete differential operators containing only the unknown spatially-varying Young's modulus. This approach leads to a set of algebraic equations which can be solved for the spatial distribution of Young's modulus.

Results:

Figures 1 and 2 show the regular plane wave that might be expected in a simple bar. However, if the sides of the bar are allowed to vibrate freely, the more complex wave pattern shown in figures 3 and 4 is generated even is this simple geometry. The wave patterns that develop are very sensitive to the boundary conditions.

Figures 5 and 6 shows the breast image and the model used for the remainder of the simulations. Figures 7 and 8 show the vibrations resulting in a homogeneous breast. The pattern of

vibration is complicated because the geometry is not regular. Figures 9 and 10 show how sensitive the solution is to the value of the Young's modulus of the glandular tissue. The pattern of vibration changes completely when the Young's modulus changes from 2 times the Young's modulus of fat to 10 times.

It is also worth noting that both distortional and dilational waves are both present in both the shaking vibrations in Figure 9 and in the shear vibrations in Figure 10. In Figure 9 the dilational waves are in the x direction and the distortional waves are in the y direction. The Distortional waves have a much shorter wavelength. In Figure 10 with a shear excitation, the waves are simply switched in direction.

Figures 11 - 13 show the waves when the boundaries are unconstrained. The pattern of waves changes dramatically from the constrained boundary conditions shown in Figures 7 and 8.

The effects of damping are demonstrated in Figures 14 - 16. The damping primarily affects the shear waves that are moving up and down in the image. The damping of the shear waves may lead to the use of shaking or squeezing rather than shear waves to vibrate the tissue.

Figure 17 shows the results of the reconstruction of the elasticity from the calculated displacements. The reconstruction is an excellent match to the original model.

Conclusions:

Tissue motion during even simple vibrations is very complicated and is sensitive to a wide variety of factors ranging from the geometry to the boundary conditions. Both distortional and dilational waves are produced in any heterogeneous or irregularly shaped breast. The complex wave patterns require a partial differential equation (PDE) based solution because simple plane waves solutions rarely occur. However, simple reconstruction's from the PDE are possible. Further work is required to explore those methods.

The effects of damping indicate that dispersive effects are important to measure. They may very well be useful in tissue differentiation but they are necessary for accurate reconstruction. Multi-frequency excitations are needed to estimate the dispersive effects.

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